

TITLE: Small organic compounds for modulation of cholesterol transport via regulation of the scavenger receptor SR-BI for HDL

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CA 2501685	A1	20040422	CA 2003-2501685	20031008
AU 2003288925	A1	20040504	AU 2003-288925	20031008
US 20040171073	A1	20040902	US 2003-681746	20031008
EP 1562605	A2	20050817	EP 2003-781314	20031008
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006515274	T	20060525	JP 2004-543548	20031008
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AB Methods for regulation of lipid and cholesterol uptake are described which are based on regulation of the expression or function of the SR-BI HDL receptor. The examples demonstrate that estrogen dramatically down-regulates SR-BI under conditions of tremendous upregulation of the LDL-receptor. The examples also demonstrate the upregulation of SR-BI in rat adrenal membranes and other non-placental steroidogenic tissues from animals treated with estrogen, but not in other non-placental non-steroidogenic tissues, including lung, liver, and skin. Examples further demonstrate the uptake of fluorescently labeled HDL into the liver cells of animal, which does not occur when the animals are treated with estrogen. Examples also demonstrate the in vivo effects of SR-BI expression on HDL metabolism, in mice transiently overexpressing hepatic SR-BI following recombinant adenovirus infection. Overexpression of the SR-BI in the hepatic tissue caused a dramatic decrease in cholesterol blood levels. These results demonstrate that modulation of SR-BI levels, either directly or indirectly, can be used to modulate levels of cholesterol in the blood. Over 200 small organic compds. are identified that alter the transfer of lipids between HDL and cells mediated by the HDL receptor SR-BI, cellular and selective lipid uptake of HDL cholesteryl ether, and efflux of cellular cholesterol to HDL; several compds. have IC50 values in the micromolar or lower range. They specifically alter SR-BI binding, as they required the expression of active SR-BI receptors and they did not interfere with several

clathrin-dependent and independent endocytic pathways, the secretory pathway, nor the actin- or tubulin cytoskeletal networks. Strikingly, inhibition of lipid transfer was accompanied by enhanced HDL binding affinity (reduced dissociation rates).

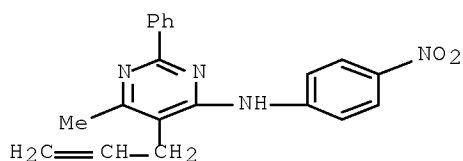
IT 330819-79-9

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

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RN 330819-79-9 HCAPLUS

CN 4-Pyrimidinamine, 6-methyl-N-(4-nitrophenyl)-2-phenyl-5-(2-propen-1-yl)- (CA INDEX NAME)



IC ICM A61B

CC 1-8 (Pharmacology)

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